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ON THE PATHOLOGY OF NIGHT-SWEATING IN PHTHISIS,

AND THE MODE OF ACTION OF STRYCHNIA AND
OTHER REMEDIES IN IT.

BY

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After the night-sweats which occur in phthisis the patients are very exhausted, and not unfrequently feel a certain soreness of the limbs similar to that which occurs in healthy persons after great exertion. The exhaustion produced by the sweating is sometimes attributed to the actual loss of material from the body in the perspiration, but this can hardly be the case, as the amount of nutritive matter contained in the sweat is very small, and we notice that the perspiration which occurs in healthy persons after exertion does not cause any feeling of weakness. It occurred to me, therefore, that instead of the sweating being the cause of the exhaustion in phthisis, the exhaustion and the sweat were both consequences of one common cause. In order to discover what this cause may be, it may be well to proceed to track, as it were, the process of sweating backwards, until we find some condition that may account both for it and for the weakness. Now, the production of sweat is due to the functional activity of the secreting cells in the sweat glands, which remove from the blood a quantity of water and salts, and pour it out upon the surface of the skin. For the functional activity of these cells two things are requisite: the one is a supply of blood to them which will provide them with the fluid necessary to form the sweat; the second is the nervous stimulus imparted to them by the secreting nerves, which excites them to functional activity. It is only recently that the importance of these nerves as a factor in the secretion of sweat has been fully recognised, although various circumstances seemed to point to the fact that

sweat was not dependent merely upon a full supply of blood to the sweat glands. In the perspiration which follows active physical exercise, we no doubt find that the skin is suffused with blood, and the sweat glands are therefore richly supplied with it. But in fever we not unfrequently find that the skin is even more suffused with blood, as is shown by its redness, so that the glands may have an abundant supply, and yet, notwithstanding this, the skin, instead of being covered with sweat, is perfectly dry. This shows, then, that a free supply of blood alone is insufficient to induce perspiration. On the other hand, we find that perspiration may occur freely when the supply of blood is exceedingly scanty. In persons stricken with sudden fear, or in those at the point of death, we find that the skin is pallid or livid, the surface cold, indicating that the supply of blood to it is very scanty, and yet at this very moment it may be bedewed with heavy drops of perspiration. This fact shows that perspiration may occur with a scanty supply of blood. The facts are exactly analogous to what we find in the secretion of saliva by the submaxillary gland. In this gland, irritation of the chorda tympani nerve causes dilatation of the vessels of the gland, a copious supply of blood to it and a free secretion of saliva. Irritation of the sympathetic nerve also causes secretion of saliva, but instead of the vessels being widely dilated and the circulation in the gland rapid and free, the vessels are contracted and the circulation is very slow. We find, also, that there is a similarity between the secretion of saliva and the secretion of sweat, not only in the nervous conditions under which they may occur, but in the way in which they are affected by various drugs. The effect of atropine, for example, upon the submaxillary gland, is to paralyse the ends of the secreting nerves in the glandular structure, and the consequence of this is, that when the chorda tympani is irritated after the administration of a dose of atropia, the vessels of the gland dilate as usual, blood flows freely through it, but, the secreting nerves having been paralysed, the secreting cells take up nothing from the blood, and not a drop of saliva flows from the duct. When, on the contrary, calabar bean is administered, the effect is strikingly different, for its action is not to paralyse, but to stimulate the secreting nerves. In consequence of this, the secreting cells begin actively to take fluid from the blood and to pour it out through the duct of the gland in the form of saliva. But this process does not last long, for the bean has a second action. Its stimulating power is not confined to the secreting nerves of the gland, but extends also to the vaso-motor nerves which regulate the calibre of the blood-vessels which supply it.

These vaso-motor nerves, being stimulated by the drug, cause the vessels to contract to such an extent as to cut off the supply of blood from the glands almost entirely. The secreting cells are thus deprived of the material from which the saliva ought to be formed, and thus, notwithstanding the functional activity which they are exerting under the stimulus of the secreting nerves, the formation of saliva very shortly comes to an end. In persons who are poisoned with belladonna it has been observed that the vessels of the skin were much dilated, so that the skin itself was covered with a scarlet flush, notwithstanding which the surface was dry. This dryness was not confined to the skin, but extended to the mouth, and it was caused both in the mouth and on the skin by the paralysis of the secreting nerves of the salivary and sweat glands produced by the drug. Calabar bean, on the contrary, causes a certain amount of salivation and cold sweats; and other drugs, such as pilocarpine, which does not, like calabar bean, limit its own action upon the secreting cells of the salivary glands by lessening their blood supply, causes very profuse salivation as well as profuse sweating. Now the action of pilocarpine is exerted upon the terminations of the secreting nerves in the salivary and sweat glands, and does not seem to be dependent upon any action on the nerve centres. But although pilocarpine may stimulate the sweat glands by acting upon the ends of the secreting nerves within them, it is probable that, in ordinary circumstances, the secretion is regulated, not by the condition of the terminal filaments of the secretory nerves, but by the nerve centres acting on the glands through those nerves. The nerve centres for the secretion of sweat lie partly in the spinal cord and partly in the medulla oblongata. In this respect they resemble two other important nerve centres, viz., the centre for respiration, or respiratory centre, and the vaso-motor centre—the respiratory centre, by which the respiratory muscles are innervated and the respiratory movements kept up, and the vaso-motor centre, from which stimuli constantly proceeding to the vessels keep them in a state of chronic contraction.

Both these centres were formerly supposed to be situated in the medulla oblongata alone, because when the medulla was separated from the cord by a transverse cut at the level of the occiput, respiration ceased, and the tonic contraction of the vessels in the body at once ceased, and they became dilated.

It was first shown by Schiff, however, that if part of the medulla were destroyed, so as to cause the respiratory movements completely to cease, the death of the animal, which would usually occur under such conditions, might be prevented by the

continuous use of artificial respiration for many hours. By this process time was allowed for the remaining portion of the medulla to learn, as it were, how to perform the function of the part which had been destroyed, as well as its own, so that after artificial respiration had gone on for several hours, the animal began to make feeble attempts to breathe, and these became stronger and stronger, until at last respiration was again established. It was thus shown that when a part of the respiratory centre in the medulla was destroyed, the remainder might become sufficiently powerful to perform the functions of the whole; but the experiments of Prokop Rokitanski have shown that, instead of being limited to the medulla oblongata, as was formerly supposed, the respiratory centre actually extends for some distance down the spinal cord. When the medulla is completely separated from the cord by a transverse cut of the level of the occiput, respiratory movements usually cease, and do not recommence. But if strychnia be injected into the circulation immediately after the cord has been divided, the respiratory movements again commence. It is evident that these movements in this case do not depend upon the action of the medulla at all, as they did in the experiments of Schiff, for here the whole of the medulla has been cut off from any connection with the respiratory muscles, and the respiratory movements must therefore depend upon stimuli proceeding to the respiratory muscles, not from the medulla oblongata, but from the spinal cord. It is clear, then, from these experiments, that the respiratory centre is not confined to the medulla oblongata, but extends to the spinal cord. Usually, however, the spinal part of it is too weak to keep up the respiratory movements alone without the aid of the medullary part, and can only do so when it is stimulated to excessive action by means of strychnia. This conclusion is also borne out by the fact that when strychnia is given to an animal before the division of the cord at the occiput, the respiratory movements do not entirely cease at the moment of division, as they usually do. And what is true of the respiratory hold also with regard to the vaso-motor centre. When the cord is divided at the occiput, the vessels, being no longer under the influence of the vaso-motor centre, usually dilate. But here also, after the injection of the strychnia, vaso-motor power is restored, and the vessels again contract to a greater or less extent. It is evident, then, that the vaso-motor centre, like the respiratory, extends a certain distance down the cord, and that it also, like the respiratory centre, is stimulated to increased action by strychnia.

Closely associated with these two centres appear to be the

sweat centres. It was first observed by Goltz that irritation of the sciatic nerve would produce sweating in a limb, and it was shown by Kendall and Luchsinger that this sweat was independent of any alteration in the vascular supply, for it occurred in animals poisoned with curare, where all the vessels going to the limb had been tied; and it even occurred in an amputated leg for a quarter of an hour after its severance from the body. The nerve centres by which the sweat nerves are usually excited were localised by Luchsinger in the spinal cord, but Nawrocki, who repeated his experiments, came to the conclusion that the sweat centre was situated not in the spinal cord, but in the medulla oblongata, because he found that division of the spinal cord high up arrested the secretion of sweat. The reason of this discrepancy between the conclusions of Luchsinger and Nawrocki probably is that the sweat centre, like the respiratory and vaso-motor centres, is not confined either to the medulla or to the chord, but extends through both. It is probable that, like the respiratory and vaso-motor centres, a great portion of the sweat centre is situated in the medulla, and in Nawrocki's experiments, when the influence of this part was destroyed by section of the cord, the perspiration ceased, just as respiration and vascular tone are also destroyed under ordinary circumstances. It is probable, however, that in Luchsinger's experiments the spinal portion of the vaso-motor centres was sufficiently powerful to excite perspiration, even after the separation from the medulla. These centres were found by Luchsinger to be excited, and perspiration produced by increased temperature of the blood, by increased carbonic acid in the blood, and also by nicotine which had been introduced into the circulation. Increased temperature, as we well know, causes sweating, usually accompanied with dilatation of the vessels of the skin, as when we are exposed to a hot sun or get warm from exertion. Tobacco, on the other hand causes sweating with diminished supply of blood to the skin, the countenance becoming exceedingly pale at the same time that a cold sweat breaks out, as most young smokers find out by sad experience. The effect of increased carbonic acid in the blood is visible in the cold sweats which bedew the brows of dying persons. I have watched the process, and have observed that it was just as the finger-nails, the lobes of the ears, and the lips began to get livid that the sweat drops began to appear on the forehead. It was a consideration of this fact which led me to suspect that the sweats of phthisis might be due to accumulation of carbonic acid in the blood stimulating the sweat centres. Nor would it do this only, for any imperfect aeration of the blood would lead to imperfect

oxidation of the products of tissue waste in the body, and their consequent accumulation would produce the same soreness and lassitude which come on from the accumulation through over-production by excessive muscular exertion. But it may be said, How is it that carbonic acid comes to accumulate in the blood in this way? In a healthy person no such accumulation takes place, because, although carbonic acid in the blood acts as a stimulus to the sweat centres, the vaso-motor centres, and the respiratory centres, yet the latter are more susceptible than the two former, so that whenever a slight increase of the amount of carbonic acid in the blood occurs, the respiratory centre is stimulated, the respiratory muscles are thrown into increased action, and the blood being more aerated, the amount of carbonic acid in it is once again reduced to the normal. But supposing the respiratory centre is weakened in any way so as to become less sensitive to the stimulus of carbonic acid in the blood than the other two centres, this will no longer be the case, and then we shall find cold perspirations occur. This is the condition which I believe to be present in phthisis. The constant stimulation of the respiratory centre by the irritation in the lungs, and the violent respiratory efforts which occur in coughing, so exhaust the irritability of this centre, especially during sleep, that it no longer responds in the normal manner to the stimulus of carbonic acid in the blood. The blood may thus become more and more venous, until the carbonic acid in it excites the sweat centres, and possibly also the vaso-motor centres, before the respiratory centre begins to respond.

This, then, I believe to be the pathology of night-sweating in phthisis. The respiratory centre becomes exhausted by the reflex irritation from the lung, so that it no longer responds so readily as it ought to the stimulus directly applied to it by carbonic acid in the blood circulating through the medulla and through the spinal cord. In consequence of this the blood becomes more or less venous, and to this venosity, and the consequent imperfect tissue change, and not, as was formerly supposed, to the actual loss of fluid or sweat in the sleep, are the nervous and muscular exhaustion and prostration observed in night-sweats to be attributed. If this pathology were correct, it occurred to me that night-sweating might be prevented by administering some remedy which would increase the excitability of the respiratory centre. Now, such a remedy exists in strychnia, as has been shown by Rokitanski's experiment. If then, a dose of strychnia or nux vomica were administered at bedtime, the excitability of the respiratory centre ought to be so much stimulated that any excess of carbonic acid would

excite it to increased action, and thus the accumulation of carbonic acid in the blood would be prevented, and the sweat, which I have supposed to be the consequence of such accumulation, would be arrested.

On proceeding to try it in the wards of St. Bartholomew's Hospital, this expectation was realised, as the following cases will show :—

CASE I.

Mary W. was admitted to Elizabeth Ward, July 10, 1879. Her confinement, four months previously, had been followed by septicæmia, after which signs of phthisis were developed. In the middle of August, when both lungs were much diseased, she suffered severely from night-sweats.

Ten drops of tincture of *nux vomica* in a little water were given at bedtime on the 10th of August, and repeated every night for a fortnight. There were no night-sweats during this time.

On the 24th of August and the next few days the dose was omitted. Each night the patient complained of sweating. After this the drug was again given at the same time and in the same quantity, and as long as it was taken there were no night-sweats until a few days before death, when it seemed to lose its effect.

In this case cough was not very troublesome, and the drug seemed to make no difference to it.

CASE II.

Lucy R., a patient in Elizabeth Ward during August and September 1879, had tubercular disease of the lungs and intestines, and suffered much distress from night-sweats.

On the 2d of September five drops of the tincture of *nux vomica* were given in a little water at bedtime.

The patient did not sweat at all that night, but she said that her cough, which was always troublesome, was worse than usual. The same dose was repeated for a few nights, with the same result—no sweats, but, as the patient thought, increase in cough.

On the 8th of September fifteen drops of laudanum were given along with fifteen drops of tincture of *nux vomica*. After the dose there was again no sweating, but the patient complained of her cough.

As long as this dose was given there were no sweats, and the cough remained much as it had been before any *nux vomica* had been given.

CASE III.

Frances E., aged 44, came to Elizabeth Ward on the 13th of August 1879, suffering from advanced phthisis. Sweating at night had been very severe for some weeks.

On August 14, fifteen drops of tincture of nux vomica were given at night. The sweating, however, was quite as bad as usual.

On the 16th the dose was increased to twenty drops. Still there was no difference in the sweating.

On the 18th twenty-five drops were given. That time, for the first time for weeks, there was no sweating. This dose was repeated every night, with the result apparently of stopping the sweats. On August 30, however, and following nights, they recurred in spite of the drug.

On the 1st September the dose was increased to thirty drops. On this night there was no sweating. This dose was repeated every night, but on the 14th of September the sweating recurred, and continued without being diminished by the drug, which was then discontinued. Some time later the sweating became very distressing in the daytime as well as at night, beginning early in the afternoon. A subcutaneous injection of extract of belladonna, gr. $\frac{1}{3}$, was then tried, given when the sweating began, with the effect of checking it in a few hours.

CASE IV.

Charles W., aged 23, was a patient in John Ward during July, August, and September 1879, with a large serous effusion into the left pleura, displacing the heart and causing considerable dyspnoea and cough. He complained very much of night-sweats. Ten drops of tincture of nux vomica were tried on the 29th of August. The patient did not sweat that night at all. The dose was continued every night with the same result, but on September 11th the sweating recurred. The dose was increased to twenty drops, and after this there was no sweating.

But it is evident that if strychnia increases the excitability of the respiratory centre by stimulus applied directly to it, such as the carbonic acid present in the blood, it is likely also to increase its susceptibility to reflex irritation, such as the exciting by tubercle in the lungs, and thus it might be that it would tend to increase the cough in case of phthisis. This, indeed, it appears, in some instances, to do. I have tried here to remedy this by a combination of strychnia with opium, and this appears partially to succeed. Where, however, strychnia does not appear

to snit, atropia may answer perfectly. Now, atropia, no doubt, acts upon peripheral terminations of the secretory nerves in the sweat glands, and thus it will altogether prevent sweating. But this is not the whole action of atropia. It has been noticed by Ringer that the beneficial action of atropia continues for a very considerable time after its administration. It seems difficult to believe that this is merely due to its action upon the sweat nerve, for it is probable that a great part of the atropia has been excreted from the body before the beneficial action which it produced has come to an end.

It seems not improbable, therefore, that the benefit derived from the employment of this drug in the night-sweating of phthisis is not due merely to its action upon the peripheral terminations of the sweat nerves, for, as has been shown by Von Bezold, it has a marked action in stimulating the respiratory centre. At the same time it lessens the irritability of the sensory nerves in the lung, and is thus likely to diminish the exhaustion of the respiratory centre, which the reflex irritation produced by the tubercle would otherwise occasion. It is to this stimulation of the respiratory centre, as much as to the paralyzing action on the respiratory nerves, that I should be inclined to attribute the benefit to be derived from atropia or from hyoscyamus, which acts almost in the same way as atropia, and is so frequently given, along with oxide of zinc, in sweating of this sort. In Dover's powder we have a combination having an action somewhat resembling that of atropia in certain respects, though differing from it very markedly in others. In health, Dover's powder is a powerful sudorific, but it frequently arrests, in the most satisfactory manner, as Dr. Murrell has shown, the night-sweating of phthisis.¹

This seems at first sight extraordinary, and yet it is quite natural if the view which I have advanced regarding the pathology of night-sweating in phthisis be correct. For the opium, by lessening the irritation from cough, will tend to prevent the exhaustion of the respiratory centre. At the same time ipccacuanha is a powerful stimulant to this centre, and thus we have in Dover's powder two of the actions that we have already observed in atropia, viz., a power of diminishing irritation from the lungs, with a power of increasing the activity of the respiratory centre. Unlike atropia, it does not paralyze the peripheral terminations of the secretory nerves in the sweat glands. Picrotoxine, also, has been found to be useful in night-sweating. It also is a powerful stimulant to the respiratory centre (Büchlein, *Arzneimittellehre*, 3te Aufl.), and probably it is by its

¹ Practitioner, vol. xxiii. p. 195, September 1879.

stimulating action upon this centre that it arrests sweating. But while it is probable that the night-sweats of phthisis chiefly depend upon exhaustion of the respiratory centre, and are to be arrested by stimulation of this centre, we must bear in mind that this may not be the only cause of such sweats. They may occur through stimulation of the sweating centres by increased temperature as well as by increased amount of carbonic acid in the circulating blood. In such circumstances quinine will probably be the best remedy, as Dr. Murrell has pointed out (*op. cit.*).

One of the great difficulties which we have to contend with in medicine is that of choosing the best drug in each particular case. Much may no doubt be done by very long experience, but it is hard, even for an old physician, and almost impossible for a young one. The only way in which this difficulty can be surmounted is by our obtaining an accurate knowledge of the pathology of disease, and of the mode of action of the remedies which we employ. In the night-sweat of phthisis atropia is probably the most powerful remedy which we possess, and we can well see how it should be so, for it combines the power of lessening irritability of the sensory nerves in the lung, of stimulating the respiratory centre, and of paralysing the ends of the secreting nerves in the sweat glands. But it possesses other actions which may render its employment inadvisable. It may so influence the salivary glands as to arrest their secretion, and cause very great discomfort to the patient by the dryness of the mouth thus occasioned. In such cases we may use Dover's powder, but if this, again, should interfere with digestion, we may resort to strychnia or nux vomica. The cases in which strychnia seems to be specially indicated are those in which the cough is not so violent as to be very distressing, and where the general debility and weakness of the circulation and digestion are prominent symptoms. It not unfrequently has happened, probably owing in some measure to the difficulty of obtaining correct statements from hospital patients, who are so readily influenced by any bias of the physician, that a remedy has had in the hands of its proposer a success which has not been observed by those who have tried it subsequently. It may be so with strychnia also as a remedy in night-sweating, but if this should not be the case, and it proved in the experience of others to have the same marked power of arresting the night-sweats of phthisis which it has had in the trials I have made of it, it will be interesting as being another remedy whose therapeutical use has been arrived at by a knowledge of its physiological action, and of the pathology of disease discovered by experiments upon animals.



